(54) **METHOD FOR OBTAINING DISEASE-RELATED CLINICAL INFORMATION**

(57)   A computer-implemented method for providing a clinical information, comprising receiving (105, 107) input data, wherein the input data comprises a graph representation of a plurality of disease lesions (209.1, 209.2, 209.3, 209.4) of a patient, applying (109) a trained function to the input data to generate the clinical information, wherein the trained function is based on a graph machine learning model, providing (111) the clinical information, wherein the clinical information comprises at least one information for the prediction of the disease progression, the survival or therapy response of the patient.

FIG 5

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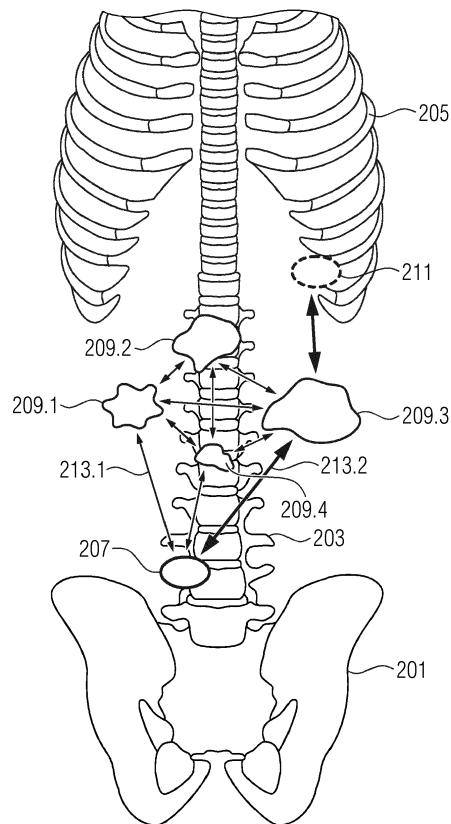
Description

[0001]   The invention is generally in the field of medical imaging and medical image analysis. Medical imaging can be performed with a variety of imaging modalities such as X-ray, ultrasound, magnetic resonance imaging (MRI), computed tomography (CT), positron-emission to-mography (PET), single-photon emission computed to-mography (SPECT) etc. as are known in the art. The imaging is performed with a respective imaging device, also referred to as "scanner".

[0002]   The spatial distribution of disease lesions of multi-focal diseases is a predictive factor for evaluating the prognosis and therapy response for such diseases.

[0003]   A well-known example for such multi-focal diseases are tumor diseases. In tumor diseases information about the primarius also known as primary tumor and metastases is an important predictive factor for disease survival and therapy response. Both global features (e.g. spatial position and relationship of primarius and metas-tases) and local features (e.g. parameters such as size, volume, texture, etc. of the primarius or individual me-tastases) are predictive factors. The primarius and the metastasis are subsequently called tumor lesions.

[0004]   With more than 1,800,000 cases and nearly 862,000 deaths per year, metastatic colorectal cancer (mCRC) is one of the leading causes of cancer related deaths in modern societies. An adequate and early as-sessment is systematically correlated with a significantly improved overall patient survival and patient wellbeing. Within tumor therapy, the approximated patient survival itself is an important variable for therapy adjustment, e.g. by adapting the medication, or escalating and deesca-lating the therapy. Thus, it contributes to an overall better patient care and patient survival. However, currently there is no established and generally accepted technique to quantitatively estimate patient survival, meaning that this estimation largely builds upon radiologic and onco-logic experience. Hence, currently the quality of the es-timation or prediction, respectively, of the patient survival time depends on the expertise of the radiologist or on-cologist.

[0005]   When looking at past efforts within medical im-aging, researchers and clinicians have focused their re-sources on estimating the survival of patients based on features like volume (Etchebehere et al., 2015) or max-imum diameter (Aoki et al., 2001) of a single tumor lesion, or the sum of these values for multiple tumor lesions (RE-CIST). These approaches assess the biology of single tumor lesions, which are important hints about the re-sponse to an intervention such as radiation therapy or chemotherapy. As this approach uses characteristics such as size or volume of selected single tumor lesions, we may say it uses local characteristics of individual le-sions.

[0006]   Furthermore, the anatomical tumor spread which relates to spatial characteristics of the spatial tu-mor lesion distribution is also predictive for survival and therapy response. As this approach uses characteristics such as distances and orientation of tumor lesions to each other we may say it relates to a global spatial dis-tribution.

[0007]   It is desirable to have a biomarker system that combines the two clinical research paths as defined above. Biomarkers are measurable indicators of biolog-ical states or conditions of an object of interest depicted in an input image. These types of problems are suitable for analysis with artificial intelligence, e.g. machine learn-ing or deep learning. However, when choosing the com-plete image volume covering all tumor lesions as model input, this will typically lead to poor performance in prac-tice given the enormous input space dimensionality. Therefore, an advanced system that would allow a ho-listic approach to analyze global and local characteristics needs a smart data representation and suitable deep learning algorithm.

[0008]   Also, the distribution of tumors over different or-gans, i.e. the full-body tumor burden of a patient, cannot trivially be analyzed by conventional deep learning (DL) systems. This is not only due to an even larger input space dimensionality but also missing image information between image patches, e.g. if a patient has tumors of lung and liver, the regions in between are not always available as image data.

[0009]   Further multi-focal diseases of high interest are chronical obstructive pulmonary diseases (COPD). The same aspects as mentioned above for tumor diseases with regard to the plurality of tumor lesions can be ob-served in COPD with regard to panlobular emphysema or changes in the lung structure, which are indicative for pulmonary hypertension.

[0010]   In a more general aspect, the same observa-tions hold true for any multi-focal disease. Other multi-focal diseases are e.g. inflammatory diseases (e.g. rheu-matoid arthritis), degenerative diseases (e.g. Alzheimer), skin diseases, arteriosclerotic diseases etc.

[0011]   The problem to be solved by the invention is therefore to provide an advanced prediction system to estimate or predict, respectively, the disease progres-sion, patient survival or therapy response with respect to multi-focal diseases.

[0012]   In the following the solution according to the in-vention is described with respect to the claimed systems as well as with respect to the claimed methods. Features, advantages or alternative embodiments herein can be assigned to the other claimed objects and vice versa. In other words, claims for the systems can be improved with features described or claimed in the context of the meth-ods. In this case, the functional features of the method are embodied by objective units of the system.

[0013]   Unless defined otherwise, technical and scien-tific terms used herein have the same meaning as com-monly understood by one of ordinary skill in the art to which this invention belongs.

[0014]   Furthermore, in the following the solution ac-cording to the invention is described with respect to meth-

ods and systems for providing clinical information related to any multi-focal disease as well as with respect to methods and systems for training a trained function for providing the clinical information. Features, advantages or alternative embodiments here-in can be assigned to the other claimed objects and vice versa. In other words, claims for methods and systems for training the trained function for providing the clinical information can be improved with features described or claimed in context of the methods and systems for providing the clinical information, and vice versa.

[0015]   In particular, the trained function of the methods and systems for providing the clinical information can be adapted by the methods and systems for training the trained function for providing the clinical information. Furthermore, the input data can comprise advantageous features and embodiments of the training input data, and vice versa. Furthermore, the output data can comprise advantageous features and embodiments of the output training data, and vice versa.

[0016]   In general, a trained function mimics cognitive functions that humans associate with other human minds. In particular, by training based on training data the trained function is able to adapt to new circumstances and to detect and extrapolate patterns.

[0017]   In general, parameters of a trained function can be adapted by means of training. In particular, supervised training, semi-supervised training, unsupervised training, reinforcement learning and/or active learning can be used. Furthermore, representation learning (an alternative term is "feature learning") can be used. In particular, the parameters of the trained functions can be adapted iteratively by several steps of training.

[0018]   In particular, a trained function can comprise a neural network, a support vector machine, a decision tree and/or a Bayesian network, and/or the trained function can be based on k-means clustering, Q-learning, genetic algorithms and/or association rules. In particular, a neural network can be a deep neural network, a convolutional neural network, a convolutional deep neural network or a graph machine learning model. Furthermore, a neural network can be an adversarial network, a deep adversarial network and/or a generative adversarial network.

[0019]   In particular, a convolutional neural network is a deep learning neural network frequently applied in image analysis. It comprises at least an input layer, at least one convolutional layer, at least one pooling layer, at least one fully connected layer and an output layer. The order of the layers can be chosen arbitrarily, usually fully connected layers are used as the last layers before the output layer.

[0020]   In one aspect the invention relates to a computer-implemented method providing a clinical information, comprising receiving input data, wherein the input data comprises a graph representation of a plurality of disease lesions of a patient, applying a trained function to the input data to generate the clinical information, wherein the trained function is based on a graph machine learning model, and providing the clinical information, wherein the clinical information comprises at least one information for the prediction of the disease progression, the survival, or therapy response of the patient.

[0021]   The term "prediction of the disease progression, the survival, or therapy response" of a patient, as used here-in, is meant to include both a prediction of an outcome of a patient undergoing a given therapy and a prognosis of a patient who is not treated. The term "prediction of the disease progression, the survival, or therapy response" may, in particular, relate to the probability of a patient undergoing an event, such as, but not limited to, disease-free survival, progression free survival, remission, occurrence of disease progression, occurrence of spread of disease lesions (e.g. metastasis) or occurrence of death, preferably within a given time frame.

[0022]   The at least one information for the prediction of the disease progression, the survival or therapy response of the patient can comprise a qualitative information and/or a quantitative information, such as a score. The term "therapy response" of a patient, as used herein, relates to the effectiveness of a certain therapy in a patient, meaning an improvement in any measure of patient status, including those measures ordinarily used in the art, such as overall survival, progression free survival, recurrence-free survival, and the like.

[0023]   A graph machine learning model is a model trained by machine learning, which generally uses data represented in the form of graphs as input data or, generally speaking, uses machine learning based on graphs or a graph representation.

[0024]   The input data comprising the graph representation of the plurality of disease lesions of the patient can be provided in any suitable form to which the trained function based on a graph machine learning model can be applied. In particular, and as an example, the graph representation can be expressed in the form of matrices encoding an information of the graph representation. In other words, the graph representation does not need to be displayed visually in the form of a graph. Alternatively, the graph representation can be a conventional graph within a coordinate system encoding the plurality of disease lesions and their information.

[0025]   In particular, at least part of said input data can be derived from imaging data of a region of interest of the patient's anatomy. Imaging data can comprise raw data, a reconstructed image and/or a mathematical or data-based representation of an image.

[0026]   According to an exemplary embodiment of the invention, the graph representation of the plurality of disease lesions can comprise disease lesions which can be spread over a patient's body.

[0027]   According to an alternative exemplary embodiment of the invention, the graph representation of the plurality of disease lesions can comprise disease lesions which can be spread over several organs.

[0028]   For these purposes, it is not necessary to have medical images of the body parts in between the different

disease lesions. In other words, the body parts in between the disease lesions can be excluded by the graph representation of the plurality of disease lesions without losing information. In other words, the body parts in between the single disease lesions are not necessary for providing the clinical information. The body parts in between the single disease lesions contain unrelated information for disease diagnosis. That means that it is sufficient to have a plurality of image patches comprising each disease lesion at least once.

[0029] According to a further alternative exemplary embodiment of the invention, the graph representation of the plurality of disease lesions can comprise disease lesions which can be spread over one particular organ (e.g. tumor lesions only in the liver, or COPD lesions only in the lung).

[0030] The clinical information can be any clinical information related to any multi-focal disease. The clinical information can be any information that can be used by a physician to decide about further therapy or palliative care of the patient.

[0031] According to an exemplary embodiment of the invention, the disease can be a tumor disease and the plurality of disease lesions can be a plurality of tumor lesions. In particular, the plurality of tumor lesions can include the primarius, also called the primary tumor, and/or the metastases.

[0032] According to a further exemplary embodiment of the invention, the plurality of disease lesions can be a plurality of lesions indicating a COPD. In this case the plurality of disease lesions can in particular comprise panlobular emphysema or changes in the lung structure, which are indicative for pulmonary hypertension.

[0033] According to an exemplary embodiment of the invention, the graph machine learning model is a graph neural network, especially a graph convolutional neural network. According to a further exemplary aspect of this embodiment of the invention, the graph machine learning model is trained by supervised training.

[0034] Encoding a plurality of disease lesions by a graph representation is useful for further analysis of the clinical-related predictive factors. This graph representation can serve as input for a graph machine learning model. By encoding the plurality of disease lesions by a graph representation missing images in between single disease lesions of the plurality of disease lesions are not a problem. The graph representation does not need any information about the body parts in between the single disease lesions. Hence, the full-body disease burden of a patient can be analyzed by the graph machine learning model without the necessity of having a complete medical image of the whole patient or at least of the whole body part which is affected by the disease lesions. The efficiency of the calculation of the clinical information can be optimized by encoding the plurality of disease lesions by a graph representation because the unnecessary information which is included in medical images is not encoded in the graph representation. Unnecessary infor-

mation is for example information of the body parts in between single disease lesions and/or further information that is comprised in medical images in addition to the information about the plurality of disease lesions. Hence, the determination of the clinical information can be accelerated by using a graph representation of the plurality of disease lesions in combination with a graph machine learning model as only information which is relevant for determining the clinical information is processed. Furthermore, it is easier for the graph machine learning model to be trained properly if the provided input data does not contain too much unrelated information.

[0035] According to a further possible aspect of the invention the graph representation of the plurality of disease lesions comprises information about a global feature of each disease lesion of the plurality of disease lesions.

[0036] In particular, a global feature of a disease lesion describes its relationship to other disease lesions or other patient organs or anatomical landmarks. Such a global feature can therefore comprise information about the spatial relationship of a given disease lesion to another disease lesion or to an anatomical landmark. In other words, connections between all or a subset of the plurality of disease lesions can be expressed by the global feature. Advantageously, a global feature of a disease lesion can describe its influence on the other disease lesions of the plurality of disease lesions and/or its influence on the surrounding anatomy. In return a global feature of a disease lesion can describe how the disease lesion is influenced by another disease lesion and/or by its position within the patient's anatomy. A global feature can be derived from imaging data of a region of interest of the patient's anatomy. In particular, the graph representation can comprise more than one global feature of each disease lesion of the plurality of disease lesions.

[0037] The relationship between each disease lesion of the plurality of disease lesions is an important parameter that can be used to predict at least one of the disease progression, the survival, and the therapy response of the patient regarding a disease specific therapy. This relationship can be expressed by a global feature of each disease lesion.

[0038] According to a further possible aspect of the invention the global feature of a given disease lesion comprises information about its location within the patient.

[0039] In particular, the location of a given disease lesion of the plurality of disease lesions can be given with respect to an anatomical coordinate system. The anatomical coordinate system can be spanned by anatomical landmarks given by the anatomy of a patient. For example, an anatomic structure e.g. the heart, the kidney, the hip bone, the bronchial branches etc. can be landmarks to provide the anatomical coordinate system of a patient. This anatomical coordinate system is patient specific. It is independent of the position of a patient within a medical device like CT, MRT, PET, SPECT etc. Hence, uncer-

tainties of positioning a patient within a medical device can be neglected by using an anatomical coordinate system. In other words, the anatomical coordinate system only depends on the anatomy of a particular patient. It is independent of the medical device with which the patient is measured or the room where the patient is. In particular, the anatomical coordinate system can be normalized. That means that the distance between two landmarks is normalized to a specific distance for all patients.

[0040] According to a preferred embodiment, for all patients the same landmarks can be chosen to define the anatomical coordinate system. Thus, the distances between the landmarks can be normalized for all anatomical coordinate systems of a plurality of patients. Like this, the normalized anatomical coordinate systems are comparable for different patients. According to an exemplary embodiment of the invention, for each of the plurality of disease lesions the global feature comprises information about its location within a patient. Determining the locations of a plurality of disease lesions with respect to a normalized anatomical coordinate system, it is easier to compare the spatial distributions of a plurality of disease lesions of different patients, who are of different sizes and weights. The global feature comprising the location of a given disease lesion can be given by an absolute value of the given single disease lesion within the given coordinate system. Alternatively or additionally, the global feature comprising the location of a disease lesion can be given by a relative value of the location of a disease lesion in relation to the distance between two landmarks. Alternatively or additionally, the global feature comprising the location of a given disease lesion can be given by an absolute and/or relative distance with regard to the other disease lesions of the plurality of disease lesions and/or with regard to the landmarks spanning the anatomical coordinate system and/or with regard to organs of the patient. Alternatively or additionally the global feature of a given disease lesion can comprise any spatial relationship with regard to other disease lesions of the plurality of disease lesions and/or with regard to landmarks. Spatial relationships can comprise for example at least one of the following: angles, distances, connections via bloodstreams, nerves, and/or lymphatics etc.

[0041] In particular, in the case that the multi-focal disease in question is a tumor disease, the location of the tumor lesion can be given with respect to the position of the primarius within an anatomical coordinate system or a normalized anatomical coordinate system. The location can be given by a relative and/or an absolute distance of the disease lesion in question to the primarius. All distances can be normalized as described above within an anatomical coordinate system.

[0042] The global information comprising the location of the plurality of disease lesions has a high impact on the prediction of the survival or therapy response of the patient. It is advantageous to locate the lesions within an anatomical coordinate system in order to avoid uncertainties of the location due to variations of the positions of the patient within the medical device. Due to long acquisition times, radiation doses, etc. full-body scans of a patient for acquiring a medical image showing all disease lesions within one image should be avoided. For providing the location of a disease lesion within an anatomical coordinate system of a patient it is not necessary to image the whole patient. It is sufficient to have enough landmarks within the image of the disease lesion to determine its location. Hence, the spatial distribution of disease lesions which are spatially separated within a patient can be encoded in one graph representation without imaging the whole patient.

Thus, global features of disease lesions have an impact on the clinical information. By integrating at least one global feature for each disease lesion in the graph representation of the plurality of disease lesions the influence of the global feature is considered when determining the clinical information.

[0043] According to a further possible aspect of the invention, the graph representation of the plurality of disease lesions comprises information about a local feature of at least one disease lesion of the plurality of disease lesions.

[0044] A local feature describes a parameter of a given disease lesion, which is independent of the local feature of another disease lesion. In particular, the local feature can for example be the size and/or the volume and/or the structure etc. of the disease lesion in question. In particular, the local feature of a given disease lesion does not provide any information about the relationship of the given disease lesion to the other disease lesions of the plurality of disease lesions. According to an exemplary embodiment of the invention, the graph representation of the plurality of disease lesions can comprise more than one local feature for a given disease lesion. In particular, the local feature or the local features of a given disease lesion can describe all properties of the disease lesion which might be of interest for the determination of the clinical information. In particular a local feature may be provided for each disease lesion of the plurality of disease lesions.

[0045] In some cases, a local feature may not be available for all disease lesions of a plurality of disease lesions. In such cases such local feature can be included at least for a subset of the plurality of disease lesions in the graph representation. Additionally or alternatively, an arbitrary value (e.g. an average value, a neutral value, a zero-value or similar) can be included or assigned in the graph representation for a given disease lesion, for which the local feature is not available, or not necessary.

[0046] The quality of the clinical information is improved by taking at least one local feature of each of the plurality of disease lesions into account. By integrating at least one local feature for each disease lesion in the graph representation of the plurality of disease lesions the influence of the local feature is considered when determining the clinical information. In particular, the combination of local and global features of the plurality of

disease lesions enhances the prediction. It is possible to combine global and local features of a plurality of disease lesions in a very effective manner by a graph representation of the plurality of disease lesions.

[0047] According to a further possible aspect of the invention the local feature of a given disease lesion comprises a handcrafted feature and/or an automatically extracted feature, in particular a feature extracted by a deep neural network.

[0048] The local feature can be determined in particular by a skilled person respectively a physician like a radiologist, an oncologist or a pulmonologist. Alternatively, the local feature can be determined by an unlearned algorithm. An unlearned algorithm can for example be based on segmenting a disease lesion by thresholding and for example determining the number of pixels within the segmented region. Alternatively, an unlearned algorithm can be a texture-based algorithm, determining the texture of a disease lesion within a medical image. Local features determined by such a skilled person or unlearned algorithm are called handcrafted features. The skilled person or unlearned algorithm can determine handcrafted features such as radiomics and provide them as local features. Radiomics are information based on image data comprising e.g. statistical information about tissue properties, diagnosis etc. concerning the disease lesion in question. Handcrafted means that the feature is determined "by hand" by a skilled person, possibly with support by specific image analysis tools, or by an unlearned algorithm. Specific image analysis tools can be for example computer implemented tools for measuring the size of a given disease lesion or the distance between two given disease lesions or for segmenting suspicious objects within a medical image. Furthermore, a handcrafted feature can be the size, the shape or further features of a disease lesion which can be determined in a medical image.

[0049] Additionally or alternatively, a local feature can be automatically extracted. In particular it can be provided by a deep neural network. This said deep neural network is not the same as the graph machine learning model providing the clinical information. In particular, the deep neural network can be combined with the graph machine learning model. In particular, both networks can be trained in an end-to-end manner. That means, that both networks can be trained together in one step. For this purpose, the results of the deep learning network can be directly provided as input data to the graph machine learning model without any user action. The at least one local feature provided by the deep neural network can be combined with at least one global feature for each disease lesion of the plurality of disease lesions. Both the combination of the at least one local and the at least one global feature or only the at least one local feature or only the at least one global feature can serve as input for the graph machine learning model without any user action. Both networks can be trained together in a supervised manner. In this case the input data can comprise

or be based on imaging data, images, or image patches of a plurality of disease lesions of a patient and the output data can be a clinical information of a patient.

[0050] Alternatively, the deep neural network and the graph machine learning model can be trained separately. In a first step the deep neural network can be trained. The input data of the trained deep neural network can comprise or be based on imaging data of a plurality of disease lesions of a patient and the output data of the trained deep neural network can be at least one local feature for each disease lesion of the plurality of disease lesions of the patient. In a second step, the output data of the trained deep neural network can be used as input data for the trained graph machine learning model. The output data of the trained graph machine learning model can be the clinical information related to any multi-focal disease.

[0051] In particular, a local feature of a given disease lesion of the plurality of disease lesions can be determined in different ways, namely by a skilled person, an unlearned algorithm and/or by a learned algorithm, e.g. a deep neural network. It is possible to combine local features determined by either approach. With this approach the advantages of both local feature determination approaches can be combined. On the one hand, the knowledge and the intuition of a skilled person in determining a handcrafted local feature of a disease lesion can be considered. On the other hand, the results of automatic extraction, e.g. with a deep neural network, can be considered. It is advantageous to combine these aspects to describe the plurality of disease lesions by global and local features to achieve an improved result regarding the clinical information.

[0052] According to a further possible aspect of the invention, the graph representation consists of a plurality of nodes and edges connecting these nodes, wherein each node of the plurality of nodes encodes a given disease lesion of the plurality of disease lesions and comprises at least information about the local feature of said disease lesion and wherein each edge of the plurality of edges encodes an information about the global feature.

[0053] In particular, the location of each node within the graph representation of the plurality of disease lesions of a patient can correspond to the location of a corresponding disease lesion within the anatomical coordinate system or the normalized anatomical coordinate system. In other words, each disease lesion of the plurality of disease lesions of a patient can be represented by at least one node within the graph representation. According to an exemplary embodiment of the invention, the node can be located at the center of mass of the corresponding disease lesion. According to an alternative exemplary embodiment of the invention, a plurality of nodes can be distributed over the surface of the corresponding disease lesion. This facilitates the geometry-based analysis of the individual disease lesion. A corresponding disease lesion of a node means that said node encodes at least a local feature of said disease lesion

and that said node is advantageously located at the location of said disease lesion.

[0054] Each node can encode at least one local feature of the corresponding disease lesion. This local feature can be a handcrafted local feature and/or it can be automatically extracted, e.g. by using a deep neural network. In particular, each node can comprise at least more than one local feature of the corresponding disease lesion. These local features of a corresponding disease lesion can be a combination of handcrafted local features and local features determined automatically, e.g. by a deep neural network or they can be only handcrafted features, or they can be only local features determined automatically, e.g. by a deep neural network. In particular, a node can additionally encode global information like the absolute position of the corresponding disease lesion within the anatomical coordinate system or the normalized anatomical coordinate system, and/or the distance of the corresponding disease lesion with regard to the surrounding disease lesions, and/or the distance of the corresponding disease lesion to given landmarks and/or organs. The distances can be relative distances. Advantageously, each node comprises a feature regarding the localization and/or the orientation of the corresponding disease lesion within the organ it occurs. In particular, the node encodes information whether the corresponding disease lesion is placed at the front, at the back, at the left, at the right, etc. of an organ. In other words, the node can encode information where within an organ a disease lesion of the plurality of disease lesions is located and/or how it is oriented within the organ.

[0055] The edges of the graph representation of the plurality of disease lesions are encoding an information of the global feature of each disease lesion of the plurality of disease lesions. The edges connect single nodes of the graph representation, wherein not each node has to be connected with each other node of the plurality of nodes. The edges encode the relationship between the nodes of the graph representation of the disease lesions. In particular, the edges can encode the spatial configuration of the nodes. Hence, for example an edge connecting two nodes can comprise the distance between these nodes. The distance can be an absolute distance between the nodes, or it can be a normalized distance with respect to the anatomical coordinate system. Hence, the relative distance between two nodes can be given with respect to the normalized anatomical coordinate system.

[0056] For providing improved clinical information it is preferred to combine information of global and local features. This combination can be best realized in a graph representation. A graph representation of the plurality of disease lesions on the one hand allows to combine a local and a global feature of each disease lesion. On the other hand, a graph representation is an effective form to combine all relevant features for providing clinical information. Within the graph representation no unnecessary data is encoded like in medical images which always include data regarding body parts which contain no urgent information for determining the clinical information. For this purpose, the nodes and edges of the graph representation can be encoded as matrices.

[0057] According to a further possible aspect of the invention the clinical information comprises at least one classification information for the prediction of the disease progression, the survival or therapy response of the patient.

[0058] The classification information relates to the association of said patient with at least one of at least two categories. These categories may be for example "high risk" and "low risk", or high, intermediate and low risk, wherein risk is the probability of a certain event occurring in a certain time period, e.g. occurrence of metastasis, disease-free survival, and the like. It can further mean a category of favourable or unfavourable clinical outcome of disease, responsiveness or non-responsiveness to a given treatment or the like.

[0059] Alternatively or additionally, the clinical information can comprise a quantitative value, such as a regression value. A regression value is a continuous output variable which can describe e.g. the probability of the occurrence of a medical event, the survival time etc.

[0060] In particular, the clinical information for the prediction of the survival can comprise a prediction about the one-year-survival and/or about the estimated survival time of the patient. The one-year-survival can be provided as two class classification information (yes/no) or it can be provided as a percentage probability that the patient survives a defined time period, e.g. the next upcoming year. The survival time can be given in years. For example, the number of years the patient will survive with a probability of 90% can be provided.

[0061] Alternatively or additionally, the classification information can comprise information about a state classification of a disease lesion. The state classification of a disease lesion comprises for example information about the disease state.

[0062] The therapy response can comprise information about the response of the disease lesions with respect to a specific therapy, e.g. surgery, radiotherapy, chemotherapy and/or the combination of such therapies. In particular, the therapy response can comprise information about the percentage of disease lesions which vanished due to therapy and/or about the reduction in size of the disease lesions. In particular, the therapy response can alternatively or additionally comprise information about changes of the velocity of the spread and/or of the growth of the plurality of disease lesions. A combination of the prediction of the survival of the patient and of the therapy response of said patient helps to observe and qualify different therapies and helps a skilled person like a physician, a radiologist, an oncologist or a pulmonologist to find the best therapy in dependence of the predicted survival and/or the state of the patient and/or disease state etc.

[0063] Providing a classification information at least for

the prediction of the disease progression, the survival or the therapy response of the patient helps a physician to decide how to proceed further with regard to the choice of the best therapy or with regard to palliative care.

[0064] According to a further possible aspect of the invention the clinical information comprises at least a feature importance information regarding at least one local or global feature.

[0065] In general, the feature importance information describes which part of the input data contributes to what portions to the output data, in a given case to the clinical information. In particular, in a given case the feature importance information provides information which of the local and/or global feature, which can be comprised by the graph representation of the plurality of disease lesions, has the most influence on the clinical information. In particular, for combining a global and a local feature and/or for combining a plurality of global and local features for each disease lesion, the feature importance information can provide information about the influence of each feature on the provided clinical information. The feature importance information can be used to visualize the influences of the different features which are encoded in the graph representation of the plurality of disease lesions. In particular, the feature importance information can provide the information on which disease lesion of the plurality of disease lesions has the most impact on the clinical information.

[0066] In a preferred embodiment the feature importance information can be provided by a saliency map, also called attenuation map. A saliency map can especially be provided for a graph convolutional neural network.

[0067] It is of high interest to observe the influences of the different features on the outcome of the clinical information. In particular, this knowledge might enable a skilled person like a radiologist, an oncologist, a pulmonologist and/or other physician to attack the plurality of disease lesions at the most efficient point. For example, if a disease lesion in one specific localization causes the predicted survival of a patient to decrease it might be promising to remove such a disease lesion first before starting further therapy. Learning about such influences of different features of the plurality of disease lesions can enable said skilled person to decide for the most efficient therapy.

[0068] According to a further possible aspect of the invention the input data comprises a temporal series of a plurality of graph representations of the plurality of disease lesions of a patient.

[0069] In particular, a plurality of disease lesions of a patient can be observed over a longer time span for example during therapy or during palliative care. This observation can be done by taking medical images for example CT, MRT, PET or SPECT images over time, e.g. in discrete time distances. During therapy medical images of the plurality of disease lesions of a patient are taken in discrete time distances to check the development of the plurality of disease lesions. Hence, these sequences of images can be used to provide a temporal series of graph representations. From each time point a graph representation of the plurality of disease lesions can be created for example comprising a global and/or a local feature with respect to the nodes and edges of the corresponding graph representation. In particular, it can comprise more than one local and/or one global feature for each disease lesion. Hence, temporal changes of the local and global feature of the plurality of disease lesions can be observed and following these observations predictions can be made. Thus, the disease-related clinical information can comprise predictions about the future development of the plurality of disease lesions. Furthermore, the influence of therapy on the plurality of disease lesions can be observed and evaluated and can be provided via the clinical information. In other words the clinical information can comprise temporal related clinical information.

[0070] The number of graph representations of such a temporal series can be variable. A temporal series of graph representations of the plurality of disease lesions has to comprise at least one graph representation. The graph machine learning model can be trained with temporal series of graph representations of a plurality of disease lesions. Nevertheless, the trained network can be used to provide the clinical information also for a temporal series comprising only one graph representation.

[0071] Providing a temporal series of graph representations of the plurality of disease lesions takes the temporal changes of the features of the disease lesions into account. The clinical information comprising temporal related clinical information can be provided. This might enable the skilled person to decide for the most effective therapy as the temporal changes might provide further information. Furthermore, knowledge about the temporal behavior of a plurality of disease lesions might help to understand disease growth and/or changes of the plurality of disease lesions. This can help to intervene in an earlier state with the best therapy, which might help to increase the patient's survival time. Considering the known temporal behavior of the plurality of disease lesions helps to predict the future development of the plurality of disease lesions.

[0072] According to an alternative aspect of the invention the temporal development of the plurality of disease lesions can be trained by recurrent neurons. That means that the graph machine learning model can comprise recurrent neurons. Such recurrent neurons can remember what they have seen before. Thus, a temporal series of graph representations of the plurality of disease lesions can be used as input for the graph machine learning model. The recurrent neurons combine the information and can predict future temporal developments. The clinical information can comprise these future temporal developments. In this embodiment the graph machine learning model is designed as a graph neural network.

[0073] According to another alternative aspect of the

invention the changes of the disease lesions over the time are provided as a local feature of the latest graph representation in a temporal series. In other words, each node corresponding to a disease lesion of the plurality of disease lesions, for which information of earlier images is known, comprises information about the local and/or global feature of the said disease lesion at previous times. Thus, the local features of the plurality of nodes comprise temporal information of the corresponding node. For this aspect of the invention the graph machine learning model does not need to be trained with temporal series of graph representations as the information about the temporal changes of the plurality of disease lesions is provided by the features of the latest graph representation of the plurality of disease lesions.

[0074]   According to a further alternative aspect of the invention the temporal changes of the plurality of disease lesions can be provided by a so-called change graph. The graph representation of such a change graph comprises information about all previous states of the plurality of disease lesions which are known. The graph machine learning model can be trained on such change graphs. In this way information regarding temporal changes of the plurality of disease lesions can be considered for providing the clinical information.

[0075]   According to an aspect of the invention the clinical information can comprise information about the predicted location and time of occurrence of a potential future disease lesion.

[0076]   Based on the graph machine learning model predictions can be made where and when a new potential disease lesion might grow. In tumor diseases such potential future tumor lesions may be potential future metastases.

[0077]   In particular, this prediction can be provided if the previous development of the plurality of disease lesions is provided to the network. The temporal behavior of the plurality of disease lesions can be analyzed by one of the aforementioned possible aspects of the invention concerning the temporal behavior of the plurality of disease lesions.

[0078]   In particular, the prediction of the location and time of a potential future disease lesion can be made receiving just one graph representation of the plurality of disease lesions as input data. Alternatively, the prediction of the location and time of a potential future disease lesion can also be made receiving a temporal series of the plurality of disease lesions as input data. The clinical information can additionally comprise the probability value where and when a potential future disease lesion might start growing. The predicted location can be provided by absolute coordinates within the anatomical coordinate system respectively the normalized anatomical system. Alternatively, the predicted location can be an area within the anatomical coordinate system respectively the normalized anatomical coordinate system. This area can comprise a continuous variation of the probability of an occurrence of a potential future disease lesion. This var-

iation can be depicted in a colored heat map which can be superposed on an image of the patient's anatomy. In particular, the clinical information can comprise the location and time of more than one potential future disease lesion.

[0079]   The prediction of the location and time of a potential future disease lesion might help to provide therapies at an earlier time point. Additionally, it might help to understand how a plurality of disease lesions spreads and which paths the disease lesions are using for spreading, for example bloodstreams and lymphatics. Additionally, it might provide some information about which paths are most probably used by a disease lesion for spreading. For further disease research it is also of interest to know where the corresponding disease lesion might start growing. It might help to solve for example the following questions: Can the disease lesion start growing in each organ or does a specific type of disease lesions prefer some organs?, How long does it take until a potential future disease lesion starts to grow and how long does it take until it can be seen in medical images such as MR or CT or it can be observed in alternative ways like PET and/or SPECT?, How does the growth of a disease lesion depend on the age of the patient?, and similar questions.

[0080]   Such knowledge might help to understand the mechanism of disease growth and/or disease spread and to provide better and more specific therapies. Predictive therapies which consider the predicted development of the plurality of disease lesions can be provided.

[0081]   According to a further possible aspect of the invention the graph representation comprises information about a previous disease lesion.

[0082]   A previous disease lesion is a disease lesion which was present in the patient in the past, but has disappeared spontaneously or due to therapy. In particular, the previous disease lesion might have vanished due to therapy e.g. surgery, radiotherapy and/or chemotherapy or a combination thereof. The information can be comprised within the graph representation by a node which is located at the previous location of the vanished previous disease lesion. The node can comprise a local feature of the vanished previous disease lesion. The node can also comprise a global feature like the absolute location of the vanished previous disease lesion within an anatomical or normalized anatomical coordinate system or in relation to another disease lesion. The said node can comprise both a plurality of global and local features. The said node can be connected via edges with nodes which are representing still existing disease lesions. A local feature of the node representing the vanished previous disease lesion can comprise a local feature that encodes the fact that the previous disease lesion has vanished.

[0083]   According to an exemplary embodiment of the invention, more than one vanished previous disease lesion can be comprised by the graph representation. In particular, all vanished previous disease lesions can be comprised by the graph representation of the plurality of

disease lesions. In particular, in the case that the multi-focal disease in question is a tumor disease, a previous tumor lesion can be the primarius or a metastasis.

[0084] Taking the influence of vanished previous disease lesions into account might improve the provided clinical information. A vanished previous disease lesion still might have some influence on the development of the plurality of disease lesions as a whole. It even might be the reason for the growth of future disease lesions, due to the time-shift between the event that initiates the growth of a future disease lesion and the start of the growth of the future disease lesion. Thus, it is advantageous to take the influence of previous disease lesions into account via a node within the graph representation of the plurality of disease lesions and via corresponding edges connecting this node with other nodes of the graph representation.

[0085] In a further aspect of the invention the graph representation of a plurality of disease lesions comprises several subgraphs. A subgraph is a graph representation of a subset of the plurality of disease lesions.

[0086] In an exemplary embodiment a subgraph may comprise a graph representation at a given time point in a temporal series of time points.

[0087] In a further exemplary embodiment, a subset of disease lesions can be determined which comprises nodes which are located within one organ. Thus, for instance, the subset of the plurality of disease lesions located in the brain are represented by one subgraph, the subset of the plurality of disease lesions located in the liver form another subgraph, and so on. A subgraph can be used as input for the graph machine learning model in a similar fashion as the graph representation of all disease lesions of the plurality of disease lesions. Hence, the graph machine learning model can either provide clinical information with respect to only one of such subgraphs or it can provide clinical information based on the whole graph representation of all disease lesions of the plurality of disease lesions. The plurality of subgraphs can provide information about the full-body disease burden of the patient. For example, by combining subgraphs of all infested organs the disease burden of the patient as a whole can be analyzed. In this example, the single subgraphs allow to analyze the development of a subset of the plurality of disease lesions within one organ. The nodes or at least a subset of the nodes of the single subgraphs can be interconnected by edges. These edges can comprise information about the distance between the nodes of the different subsets. The distance can be given with respect to an anatomical coordinate system respectively a normalized anatomical coordinate system. The distances can be absolute and/or relative distances. The distances can refer to landmarks of the anatomical coordinate system respectively of the normalized anatomical coordinate system and/or they can refer to other disease lesions of the plurality of disease lesions and/or they can refer to organs of the patient. In the case that the multi-focal disease in question is a tumor disease the

distances can in particular refer to distances between a given metastasis and other metastases and/or the primarius.

[0088] The subdivision of one graph representation into a plurality of subgraphs for different organs allows the analysis of both the full-body disease burden as a whole by considering the whole graph representation and of the subset of the disease lesions within one organ. The latter helps to increase efficiency in calculating the clinical information, if only the development of the subset of disease lesions within one organ is of interest. Furthermore, the subsets allow to compare for example a patient who has a plurality of disease lesions only within the brain with another patient who has a plurality of disease lesions within the brain and the liver. For this purpose, only the subset of disease lesions within the brain of the second patient can be analyzed. This holds true for all organs. Hence, even if no patients in the training data set had the same configuration of affected organs as the current patient to analyze, this patient can still be analyzed if subgraphs trained for individual organs in other patients (and their mutual connections, as far as available) are combined into a graph representation for this patient.

[0089] In a further aspect the invention relates to a system for providing the clinical information, comprising a first interface, configured for receiving input data, wherein the input data comprises a graph representation of a plurality of disease lesions of a patient, comprising a second interface, configured for providing the clinical information, wherein the clinical information comprises at least one information for the prediction of the disease progression, the survival, or the therapy response of the patient and comprising a computation unit, configured for applying a trained function to the input data to generate the clinical information, wherein the trained function is based on a graph machine learning model, wherein the information is generated.

[0090] In a further aspect the invention relates to a computer program comprising instructions which, when the program is executed by a computer system, cause the computer system to carry out the method of the invention as explained above together with its potential aspects.

[0091] In a further aspect the invention relates to a computer-readable medium comprising instructions which, when executed by a computer system, cause the computer system to carry out the method of the invention explained above together with its potential aspects.

[0092] In a further aspect the invention relates to a training system, comprising a first training interface, configured for receiving input training data, wherein the input training data comprises a graph representation of a plurality of disease lesions of a patient, a second training interface, configured for receiving output training data, wherein the input training data is related to the output training data, wherein the output draining data comprises a clinical information, wherein the clinical information comprises at least one information for the prediction of

the disease progression, the survival or therapy response of the patient, a training computation unit, configured for training a function based on the input training data and the output training data, a third training interface, configured for providing the trained function.

[0093] In a further aspect the invention relates to a computer program comprising instructions which, when the program is executed by a training system, cause the training system to carry out the method explained above together with its potential aspects.

[0094] In a further aspect the invention relates to a computer-readable medium comprising instructions which, when executed by a training system, cause the training system to carry out the method explained above together with its potential aspects.

[0095] The present invention and its technical field are subsequently explained in further detail by exemplary embodiments shown in the drawings. The exemplary embodiments only conduce better understanding of the present invention and in no case are to be construed as limiting for the scope of the present invention. Particularly, it is possible to extract aspects of the subject-matter described in the figures and to combine it with other components and findings of the present description or figures, if not explicitly described differently. Equal reference signs refer to the same objects, such that explanations from other figures may be supplementary used.

Fig. 1 shows a schematic flow chart of the method for providing a clinical information.

Fig. 2 shows a schematic flow chart of the method for providing a clinical information in combination with an automatically extracted local feature of a disease lesion.

Fig. 3 shows a schematic flow chart of the method for providing a clinical information in combination with a handcrafted local feature of a disease lesion.

Fig. 4 shows a schematic flow chart of the method for providing a clinical information in combination with an automatically extracted and a handcrafted local feature of a disease lesion.

Fig. 5 shows a schematic view of the potential output of the method for providing a clinical information wherein the multi-focal disease in question is a tumor disease.

Fig. 6 shows a schematic view of the system for providing a clinical information.

Fig. 7 shows a schematic view of the system comprising the providing system for a clinical information.

[0096] In **Fig. 1** the computer implemented method for providing a clinical information also referred to as clinical information related to any multi-focal disease is schematically depicted. The method comprises the steps of receiving global features 107 of a plurality of disease lesions, receiving local features 105 of a plurality of disease lesion, applying the trained function of the graph machine learning model 109 and the step providing the clinical information 111. The steps of receiving local features 105 and of receiving global features 107 may be executed in any sequence.

[0097] In the step of receiving global features 107, information about the location of each single disease lesion of the plurality of disease lesions is provided to the network. The locations of the single disease lesions can be provided in relation to a normalized anatomical coordinate system. The plurality of disease lesions can comprise the disease burden of one organ or it can comprise the full-body disease burden. The locations of the plurality of disease lesions can be the locations determined within the plurality of medical image respectively image patches of the plurality of disease lesions. Alternatively, the locations can comprise a temporal series of locations of each of the plurality of disease lesions of several medical images of each disease lesion.

[0098] In the step of receiving local features 105, information about the local features of each disease lesion of the plurality of disease lesions is provided to the network. The local features can comprise for example the size, the structure the compactness etc. of the single disease lesion. The local features of the plurality of disease lesions can be the local features determined with the help of one medical image of each disease lesion. Alternatively, the local features can comprise a temporal series of local features of at least one local feature of the plurality of disease lesions.

[0099] The graph representation of the plurality of disease lesions is described by matrices which comprise the of global and local features received in steps of receiving local features 105 and of receiving global features 107. In this embodiment the first layer of the graph machine learning model is a graph construction layer. The matrices describing the graph representation are created in this graph construction layer based on the global and local features.

[0100] In step of applying the trained function of the graph machine learning model 109 the clinical information is determined. In a first step the local features of the plurality of disease lesions are arranged in a NxD matrix X. N is the number of nodes. In other words, N is the number of disease lesions within the plurality of disease lesions. D is the number of features per node. Thus, X encodes at least all features of each node. The features of a node comprise at least one local feature of each disease lesion. Advantageously, the features encoded in the matrix X also comprise a spatial information of each disease lesion. In a second step the spatial configuration of the plurality of disease lesions is encoded by a NxN matix A by the graph construction layer. A can be called the (weighted) adjacency matrix of the graph or a function

thereof. A encodes the global features of the plurality of disease lesions. A encodes how information is propagated between the nodes and thereby incorporates the global, spatial information. The first and the second step of the step of applying the trained function 109 can be executed in any sequence.

[0101] Advantageously, the graph machine learning model is a graph neural network especially a graph convolutional neural network comprising multiple layers. A single graph convolutional layer may be written as a function

$$f(H^l, A) = \sigma \left(A H^l W^l \right).$$

H[1] holds the features of the 1-th network layer, with X=H°. W[1] is a matrix of trainable weights, which are trained during the training respectively supervised learning procedure of the graph convolutional neural network. σ is a non-linear activation function. Stacking several of these functions, while ensuring that the spectral radius of the matrix A is normalized such that the values after multiplication do not diverge, a graph machine learning model network as described above can be obtained.

[0102] After executing the graph machine learning model, the step of providing the results 111 is executed. The results are the clinical information. The clinical information can comprise a classification information for the prediction of the disease progression, the survival and/or the therapy response. Additionally, it can comprise a feature importance information, especially a saliency map, showing which of the provided features of the plurality of disease lesions contributes most to the provided clinical information. Furthermore, the clinical information can comprise information about potential future disease lesions. It can comprise information about the potential location and the potential time when the potential future disease lesions might start growing. Additional temporal related clinical information that can be comprised by the clinical information can be trained. The clinical information can be provided in a graphical manner like exemplarily shown in Fig. 5 and as further described in connection with Fig. 5 further below.

[0103] In **Fig. 2** the computer implemented method for providing the clinical information 111 explained in relation to Fig. 1 is shown in combination with a deep neural network for providing the local features of each of the plurality of disease lesions is shown. A plurality of patches of images 101 of the single disease lesions of the plurality of disease lesions is provided to a deep neural network in step 102. The patches do not have to have any relationship. The spatial relation between the patches is determined separately. The deep neural network is applied 103.1. Advantageously, the deep neural network is a convolutional neural network encoder. The deep neural network provides the information about the local features of the plurality of disease lesions to the graph machine learning model. The steps of receiving global features

107 of a plurality of disease lesions, receiving local features 105 of a plurality of disease lesion, applying the trained function of the graph machine learning model 109 and the step of providing 111 the clinical information are executed in analogy to the description of Fig. 1. Hereby, the local information is provided by the deep neural network to the graph machine learning model.

[0104] The deep neural network and the graph machine learning model can in one embodiment have been trained together in an end-to-end manner. In this case, the input of the supervised learning is provided to the deep neural network and the output of the supervised learning is provided by the graph machine learning model. Alternatively, the deep neural network and the graph machine learning model are trained separately. In this case, two independent supervised learning algorithms are executed for each of the both networks.

[0105] The spatial configuration of the single disease lesions is determined in a separate step with the help of image patches 101 depicting the plurality of disease lesions together with anatomical landmarks. This spatial configuration is received 107 as global features by the graph machine learning model.

[0106] In **Fig 3** the computer implemented method for providing clinical information which is explained in relation to Fig. 1 is shown, in combination with an alternative approach to determine the local information. This embodiment starts by providing 102 the plurality of image patches 101 of the plurality of disease lesions to a skilled person like a radiologist, an oncologist, a pulmonologist and/or physician. The method comprises determining 103.2 handcrafted local features by eye based on the image information by the skilled person. Such a handcrafted feature can be provided via an input device or interface. In an alternative embodiment handcrafted features can be extracted by an unlearned algorithm like a texture-quantifying algorithm and/or by a segmentation algorithm. The steps of receiving global features 107 of a plurality of disease lesions, receiving local features 105 of a plurality of disease lesion, applying 109 the trained function of the graph machine learning model and the step of providing the clinical information 111 are executed in analogy to the description of Fig. 1. Hereby the local features of each of the plurality of disease lesions is provided by the skilled person to the graph machine learning model.

[0107] The spatial configuration of the single disease lesions is determined in a separate step with the help of image patches 101 depicting the plurality of disease lesions together with anatomical landmarks. This spatial configuration is received 107 as global features by the graph machine learning model.

[0108] In **Fig. 4** a combination of the embodiment shown in Fig. 2 and the embodiment shown in Fig. 3 is depicted. The image patches 101 are provided 102 to both a deep neural network and a skilled person. Both determine local features 103.1, 103.2 of each of the disease lesions of the plurality of disease lesions. These

local features of both approaches are combined and are both received 105 by a graph machine learning model. In alternative embodiments a further pre-processing might be performed to ensure that the local features of a single disease lesion are in accordance with each other and do not comprise local features twice due to the combination of the two determining 103.1, 103.2 steps. The steps of receiving global features 107 of a plurality of disease lesions, receiving local features 105 of a plurality of disease lesion, applying the trained function of the graph machine learning model 109 and the step of providing the clinical information 111 are executed in analogy to the description of Fig. 1.

The spatial configuration of the single disease lesions is determined in a separate step with the help of image patches 101 depicting the plurality of disease lesions together with anatomical landmarks. This spatial configuration is received 107 as global features by the graph machine learning model.

[0109] In **Fig. 5** an embodiment for the graphical depiction of the provided clinical information is shown. The multi-focal disease in the example is a tumor disease. Therefore, the plurality of disease lesions in this example is a plurality of tumor lesions. The clinical information is superposed on an image of a human skeleton comprising the part or region of the human body that is infested by tumor lesions. In the depicted embodiment the human skeleton comprises the hip bone 201, the spinal column 203 and the ribs 205. The plurality of tumor lesions 209.1, 209.2, 209.3, 209.4 is depicted within the skeleton. The single tumor lesions 209.1, 209.2, 209.3, 209.4 are located at the correct location within the anatomical coordinate system spanned by the human skeleton. Advantageously, the depiction of the single tumor lesions 209.1, 209.2, 209.3, 209.4 additionally shows the size and the structure of the corresponding tumor lesion 209.1, 209.2, 209.3, 209.4 in the image provided to the user. The depiction of the plurality of tumor lesions 209.1, 209.2, 209.3, 209.4 might be a segmented representation of the tumor lesions 209.1, 209.2, 209.3, 209.4 within the image patches 101. The image patches 101 are provided 102 as input data to the deep neural network and/or to the skilled person. The global features of the plurality of tumor lesions 209.1, 209.2, 209.3, 209.4 are for example depicted by the location of each single tumor lesion 209.1, 209.2, 209.3, 209.4 in relation to the human skeleton. Additionally, the global features are expressed by interconnections 213.1, 213.2 between the single tumor lesions 209.1, 209.2, 209.3, 209.4. These interconnections 213.1, 213.2 are represented by arrows. For clarity only two interconnections 213.1, 213.2 are indicated by a reference numeral. The output of the saliency map is depicted by the size and thickness of the interconnection 213.1, 213.2. The thicker an interconnection 213.1, 213.2 the more influence the corresponding interconnection has on the provided clinical information. In an alternative embodiment, the saliency map with respect to the local features can be depicted by a colour coded heatmap

which is superposed over the human skeleton (not shown in Fig. 5). It can be coloured red around tumor lesions 209.1, 209.2, 209.3, 209.4 that have a high influence on the clinical information and blue around tumor lesions 209.1, 209.2, 209.3, 209.4 that have less influence in the clinical information. The primarius 207 already vanished due to a surgery in this example. Nevertheless, it is depicted by a solid circle which is located at the former location of the primarius 207. Other vanished previous tumor lesions can be depicted in the same manner. Predicted potential future tumor lesions 211 are depicted by dashed circles at the predicted location. The solid circles of already vanished previous tumor lesions in this embodiment the primarius 207 and the dashed circles of potential future tumor 211 lesions can be different colours. These circles can be interconnected with the other tumor lesions 209.1, 209.2, 209.3, 209.4 by interconnections 213.1, 213.2 which encode the global information. Further clinical information regarding a given tumor lesion of the plurality of tumor lesions 209.1, 209.2, 209.3, 209.4 including previous tumor lesions 207 and potential future tumor lesions 211, can be provided by for example clicking onto the given tumor lesion in question. Then a further window can pop up showing further clinical information regarding the tumor lesion in question. The clinical information can comprise the local features and/or predicted information about any of the tumor lesions 207, 211, 209.1, 209.2, 209.3, 209.4. The predicted information for example can comprise information about the predicted start time of growth of a potential future tumor lesion 211. Furthermore, general disease-related clinical information like information for the prediction of the disease progression, the survival or therapy response can be displayed in further windows. The graphical depiction of clinical information of other multi-focal diseases can be based on the same principle.

[0110] In **Fig. 6** the system 600 for providing a disease-related clinical information is schematically depicted. The system 600 comprises means, like a central processing unit, a storage etc., arranged and configured to execute at least the steps 105 to 111 of the method of Fig. 1 to 4. The system 600 is a data processing system and may be implemented in a personal computer (PC), a laptop, a tablet, a server, a distributed system (e.g. cloud system) and the like. The data processing system 600 comprises a central processing unit (CPU) 601, a memory having a random access memory (RAM) 602 and a non-volatile memory (MEM, e.g. hard disk) 603, a human interface device (HID, e.g. keyboard, mouse, touchscreen etc.) 604 and an output device (MON, e.g. monitor, printer, speaker, etc.) 605. The CPU 601, RAM 602, HID 604 and MON 605 are communicatively connected via a data bus. The RAM 602 and MEM 603 are communicatively connected via another data bus. The method according to the first aspect of the present invention and schematically depicted in Fig. 1 to 4 can be loaded in form of a computer program into the RAM 602 from the MEM 603 or another computer-readable medium having stored the

respective computer program. According to the computer program the CPU executes at least the steps 105 to 111 of the method of Fig. 1 to 4. The execution can be initiated and controlled by a user (e.g. practitioner/radiologist/oncologist/skilled person) via the HID 604. The status and/or result of the executed computer program may be indicated to the user by the MON 605. The results of the executed computer program (disease-related clinical information) may be permanently stored on the non-volatile MEM 603 or another computer-readable medium. The disease-related clinical information which is based on image patches 101 of a clinical examination (e.g. different types of CT/MRI/PET/SPECT/sonography examination) for given clinical questions is determined and stored in the MEM 603. The optimal clinical examination for a given clinical question is automatically selected by the system 600 and may be output by the MON 605 and/or stored in the MEM 603.

[0111]   In **Fig. 7** the medical imaging system 700 comprising the system 600 of Fig. 6 arranged and configured to execute at least the steps 105 to 111 of the method of Fig. 1 to 4 is schematically depicted. The medical imaging system comprises means for conducting a medical imaging examination like CT, MRI, PET, SPECT and/or sonography examination. Here, as an example, the medical imaging system comprises a CT scanner 701 arranged and configured to conduct at least CT examinations. The CT scanner 701 is communicatively coupled to the system 600 and can receive the clinical examination (here type of CT examination) that has been selected based on the value for the clinical examination by the system 600. Based on the stored values of clinical examinations (e.g. different types of CT/MRI/PET/SPECT/sonography examination) for a given clinical question, which have been derived and stored by the system 600, the optimal clinical examination for the given clinical question is automatically selected and communicated to the CT scanner 701.

Claims

1. A computer-implemented method for providing a clinical information, comprising

    - receiving (105, 107) input data,
    wherein the input data comprises a graph representation of a plurality of disease lesions (209.1, 209.2, 209.3, 209.4) of a patient,
    - applying (109) a trained function to the input data to generate the clinical information, wherein the trained function is based on a graph machine learning model,
    - providing (111) the clinical information,
    wherein the clinical information comprises at least one information for the prediction of the disease progression, the survival, or therapy response of the patient.

2. Method according to claim 1, wherein the graph representation of the plurality of disease lesions (209.1, 209.2, 209.3, 209.4) comprises information about a global feature of each disease lesion (209.1, 209.2, 209.3, 209.4) of the plurality of disease lesions (209.1, 209.2, 209.3, 209.4).

3. Method according to claim 2, wherein the global feature of a given disease lesion (209.1, 209.2, 209.3, 209.4) comprises information about its location within the patient.

4. Method according to claim 2 or 3, wherein the graph representation of the plurality of disease lesions (209.1, 209.2, 209.3, 209.4) comprises information about a local feature of at least one disease lesion (209.1, 209.2, 209.3, 209.4) of the plurality of disease lesions (209.1, 209.2, 209.3, 209.4) .

5. Method according to claim 4, wherein the local feature of a given disease lesion (209.1, 209.2, 209.3, 209.4) comprises a handcrafted feature and/or an automatically extracted feature, in particular a feature extracted by a deep neural network.

6. Method according to claim 4 or 5,
    wherein the graph representation consists of a plurality of nodes and edges connecting these nodes, wherein each node of the plurality of nodes encodes a given disease lesion (209.1, 209.2, 209.3, 209.4) of the plurality of disease lesions (209.1, 209.2, 209.3, 209.4) and comprises at least the information about the local feature of said given disease lesion (209.1, 209.2, 209.3, 209.4) and
    wherein each edge of the plurality of edges encodes an information about the global feature.

7. Method according to one of the preceding claims, wherein the clinical information comprises at least one classification information for the disease progression, the prediction of the survival or therapy response of the patient.

8. Method according to one of the preceding claims, wherein the clinical information comprises at least a feature importance information regarding at least one local or global feature.

9. Method according to one of the preceding claims, wherein the input data comprises a temporal series of a plurality of graph representations of the plurality of disease lesions (209.1, 209.2, 209.3, 209.4) of a patient.

10. Method according to one of the preceding claims, wherein the clinical information comprises information about the predicted locations and time of occurrence of a potential future disease lesion (211).

11. Method according to one of the preceding claims, wherein the graph representation comprises information about a previous disease lesion (207).

12. A system 600 for providing a clinical information, comprising

- a first interface, configured for receiving 105, 107 input data,
wherein the input data comprises a graph representation of a plurality of disease lesions (209.1, 209.2, 209.3, 209.4) of a patient,
- a second interface, configured for providing (111) the clinical information,
wherein the clinical information comprises at least one information for the prediction of the disease progression, the survival, or therapy response of the patient,
- a computation unit, configured for applying (109) a trained function to the input data, to generate the clinical information,
wherein the trained function is based on a graph machine learning model.

13. A computer program comprising instructions which, when the program is executed by a computer system, cause the computer system to carry out the method of one of the claims 1 to 11.

14. A computer-readable medium comprising instructions which, when executed by a computer system, cause the computer system to carry out the method of one of the claims 1 to 11.

15. A training system, comprising

- a first training interface, configured for receiving (105, 107) input training data,
wherein the input training data comprises a graph representation of a plurality of disease lesions (209.1, 209.2, 209.3, 209.4) of a patient,
- a second training interface, configured for receiving (111) output training data,
wherein the input training data is related to the output training data,
wherein the output training data comprises a clinical information,
wherein the clinical information comprises at least one information for the prediction of the disease progression, the survival, or therapy response of the patient,
- a training computation unit, configured for training a function based on the input training data and the output training data,
- a third training interface, configured for providing the trained function.

16. A computer program comprising instructions which,

when the program is executed by a training system, cause the training system to carry out the method of one of the claims 1 to 11.

17. A computer-readable medium comprising instructions which, when executed by a training system, cause the training system to carry out the method of one of the claims 1 to 11.

Amended claims in accordance with Rule 137(2) EPC.

1. A computer-implemented method for providing a clinical information, comprising

- receiving (105, 107) input data,
wherein the input data comprises a graph representation of a plurality of disease lesions (209.1, 209.2, 209.3, 209.4) of a patient,
wherein the graph representation of the plurality of disease lesions (209.1, 209.2, 209.3, 209.4) comprises information about a global feature of each disease lesion (209.1, 209.2, 209.3, 209.4) of the plurality of disease lesions (209.1, 209.2, 209.3, 209.4),
wherein the global feature of a given disease lesion (209.1, 209.2, 209.3, 209.4) comprises information about its location within the patient,
- applying (109) a trained function to the input data to generate the clinical information, wherein the trained function is based on a graph neural network (p. 8, 1. 14-15),
- providing (111) the clinical information,

wherein the clinical information comprises at least one information for the prediction of the disease progression, the survival, or therapy response of the patient,
wherein the clinical information comprises at least one classification information for the disease progression, the prediction of the survival or therapy response of the patient.

2. Method according to claim 1, wherein the graph representation of the plurality of disease lesions (209.1, 209.2, 209.3, 209.4) comprises information about a local feature of at least one disease lesion (209.1, 209.2, 209.3, 209.4) of the plurality of disease lesions (209.1, 209.2, 209.3, 209.4) .

3. Method according to claim 2, wherein the local feature of a given disease lesion (209.1, 209.2, 209.3, 209.4) comprises a handcrafted feature, in particular a feature determined by a skilled person or an unlearned algorithm, (p. 14, 1. 4-6) and/or an automatically extracted feature, in particular a feature extracted by a deep neural network.

4. Method according to claim 2 or 3,

wherein the graph representation consists of a plurality of nodes and edges connecting these nodes, wherein each node of the plurality of nodes encodes a given disease lesion (209.1, 209.2, 209.3, 209.4) of the plurality of disease lesions (209.1, 209.2, 209.3, 209.4) and comprises at least the information about the local feature of said given disease lesion (209.1, 209.2, 209.3, 209.4) and wherein each edge of the plurality of edges encodes an information about the global feature.

5. Method according to one of the preceding claims, wherein the clinical information comprises at least a feature importance information regarding at least one local or global feature.

6. Method according to one of the preceding claims, wherein the input data comprises a temporal series of a plurality of graph representations of the plurality of disease lesions (209.1, 209.2, 209.3, 209.4) of a patient.

7. Method according to one of the preceding claims, wherein the clinical information comprises information about the predicted locations and time of occurrence of a potential future disease lesion (211).

8. Method according to one of the preceding claims, wherein the graph representation comprises information about a previous disease lesion (207).

9. A system 600 for providing a clinical information, comprising

   - a first interface, configured for receiving 105, 107 input data,
   wherein the input data comprises a graph representation of a plurality of disease lesions (209.1, 209.2, 209.3, 209.4) of a patient,
   wherein the graph representation of the plurality of disease lesions (209.1, 209.2, 209.3, 209.4) comprises information about a global feature of each disease lesion (209.1, 209.2, 209.3, 209.4) of the plurality of disease lesions (209.1, 209.2, 209.3, 209.4),
   wherein the global feature of a given disease lesion (209.1, 209.2, 209.3, 209.4) comprises information about its location within the patient,
   - a second interface, configured for providing (111) the clinical information,
   wherein the clinical information comprises at least one information for the prediction of the disease progression, the survival, or therapy response of the patient,
   wherein the clinical information comprises at least one classification information for the disease progression, the prediction of the survival or therapy response of the patient,

- a computation unit, configured for applying (109) a trained function to the input data, to generate the clinical information,

wherein the trained function is based on a graph neural network.

10. A computer program comprising instructions which, when the program is executed by a computer system, cause the computer system to carry out the method of one of the claims 1 to 8.

11. A computer-readable medium comprising instructions which, when executed by a computer system, cause the computer system to carry out the method of one of the claims 1 to 8.

12. A training system, comprising

   - a first training interface, configured for receiving (105, 107) input training data,
   wherein the input training data comprises a graph representation of a plurality of disease lesions (209.1, 209.2, 209.3, 209.4) of a patient,
   wherein the graph representation of the plurality of disease lesions (209.1, 209.2, 209.3, 209.4) comprises information about a global feature of each disease lesion (209.1, 209.2, 209.3, 209.4) of the plurality of disease lesions (209.1, 209.2, 209.3, 209.4),
   wherein the global feature of a given disease lesion (209.1, 209.2, 209.3, 209.4) comprises information about its location within the patient,
   - a second training interface, configured for receiving (111) output training data,
   wherein the input training data is related to the output training data,
   wherein the output training data comprises a clinical information,
   wherein the clinical information comprises at least one information for the prediction of the disease progression, the survival, or therapy response of the patient,
   wherein the clinical information comprises at least one classification information for the disease progression, the prediction of the survival or therapy response of the patient,
   - a training computation unit, configured for training a function based on the input training data and the output training data,
   - a third training interface, configured for providing the trained function.

13. A computer program comprising instructions which, when the program is executed by a training system, cause the training system to carry out the method of one of the claims 1 to 8.

14. A computer-readable medium comprising instructions which, when executed by a training system, cause the training system to carry out the method of one of the claims 1 to 8.

FIG 1
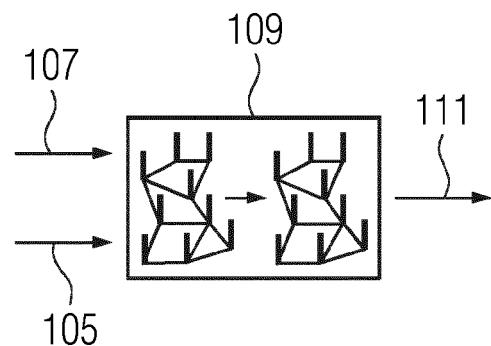
FIG 2
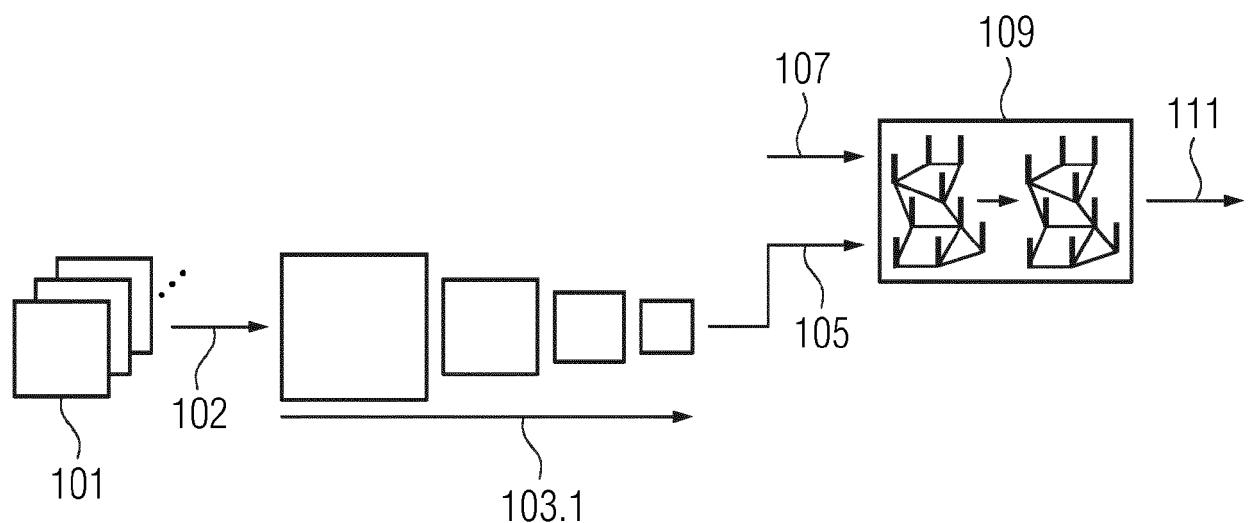
FIG 3
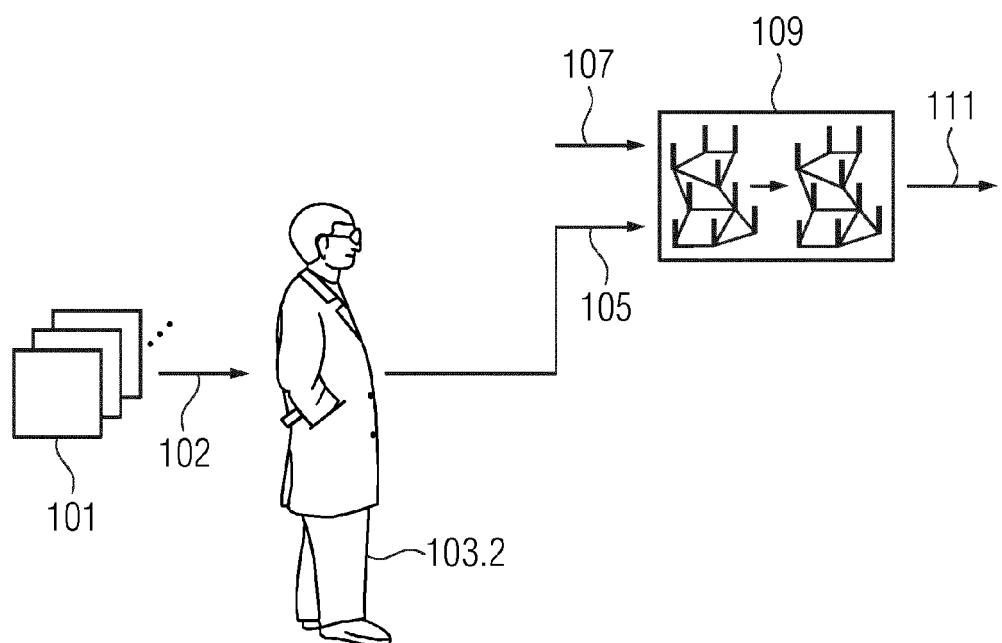
FIG 4

FIG 5

FIG 6

FIG 7

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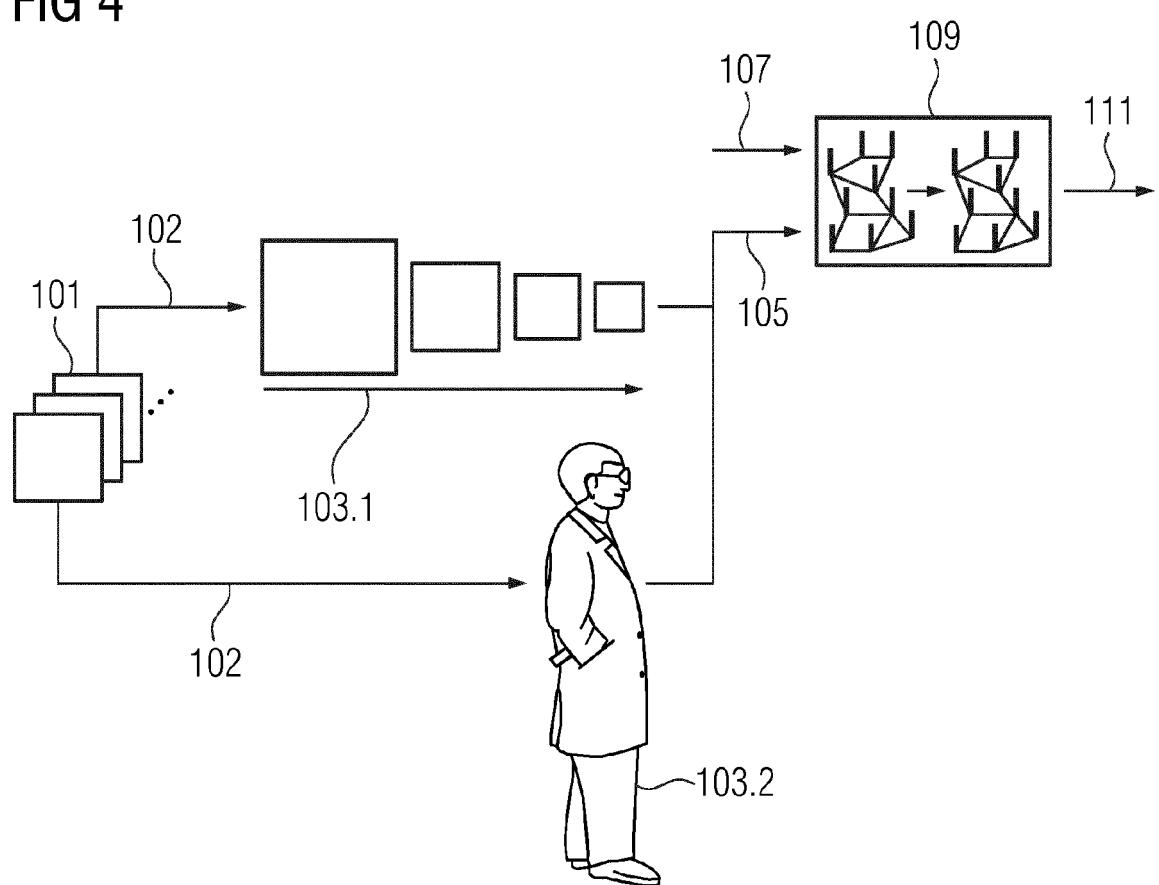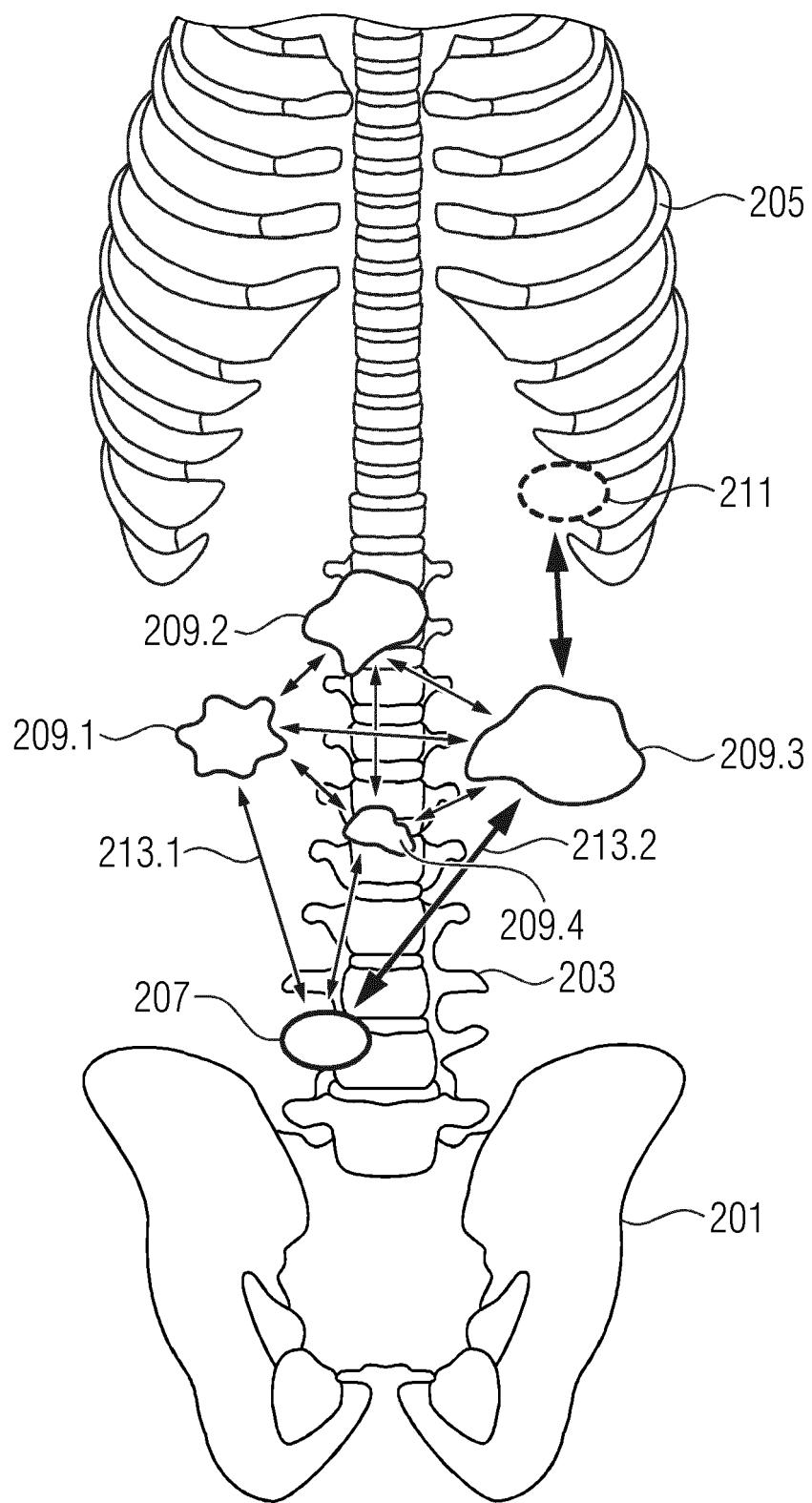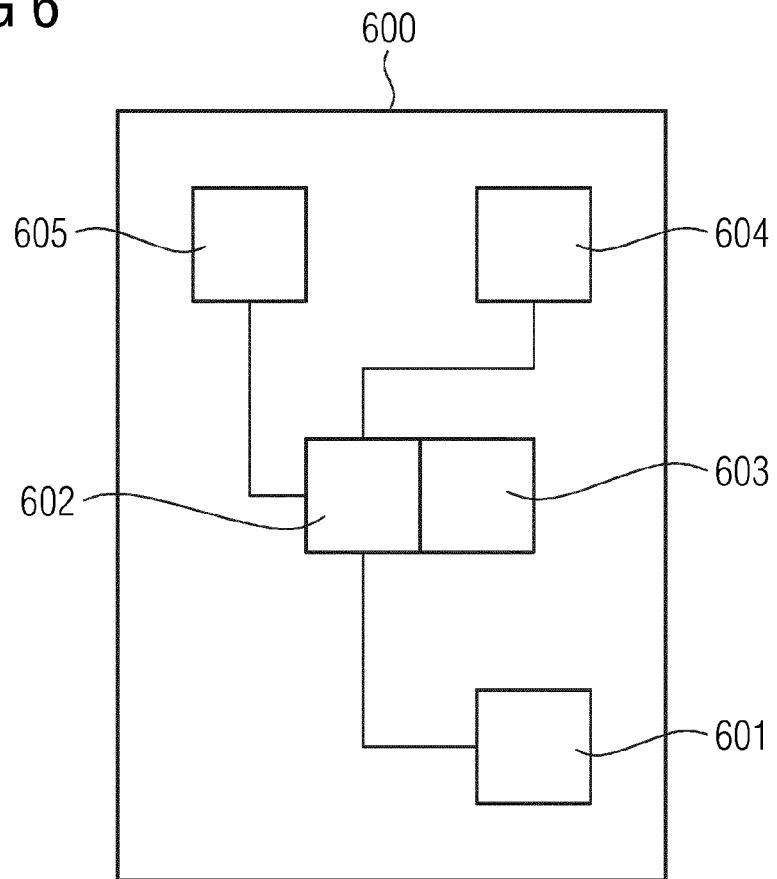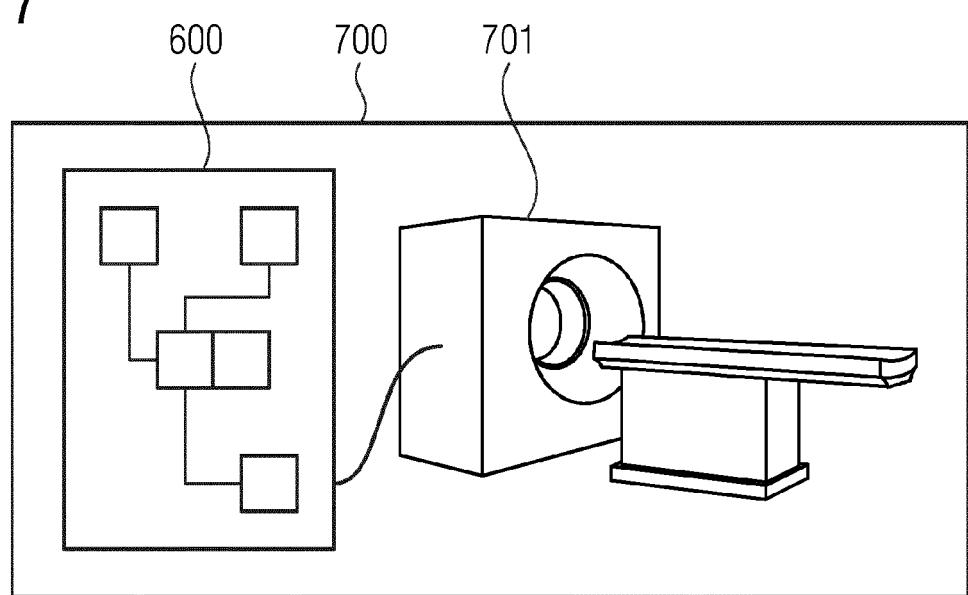
EUROPEAN SEARCH REPORT

Application Number

EP 19 21 5716

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	US 2010/057651 A1 (FUNG GLENN [US] ET AL) 4 March 2010 (2010-03-04) * paragraphs [0008], [0030], [0041] *	1-17	INV. G16H50/20 G06N3/02 G16H50/30
X	SHREY GADIYA ET AL: "Histographs: Graphs in Histopathology", ARXIV.ORG, CORNELL UNIVERSITY LIBRARY, 201 OLIN LIBRARY CORNELL UNIVERSITY ITHACA, NY 14853, 14 August 2019 (2019-08-14), XP081462232, * abstract; sections 2.1.2, 2.1.3, 2.2 *	1-17	
A	Tobias Skovgaard Jepsen: "How to do Deep Learning on Graphs with Graph Convolutional Networks", , 18 September 2018 (2018-09-18), XP055689132, Retrieved from the Internet: URL:https://towardsdatascience.com/how-to-do-deep-learning-on-graphs-with-graph-convolutional-networks-7d2250723780 [retrieved on 2020-04-24] * the whole document *	1-17	
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TECHNICAL FIELDS SEARCHED (IPC)

G16H
G06N

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	4 June 2020	Reinbold, Bernhard

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US 2010057651 A1	04-03-2010	NONE	

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